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(57) Abstract

A method of treating or preventing migraine in humans comprises administering to a patient in need thereof an effective amount of lamotrigine or a pharmaceutically acceptable salt thereof.

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NOVEL TREATMENT

The present invention provides a new medical use of a known compound.

EP-0021121 (Buroughs Wellcome) describes a class of compounds which are described as being useful for the treatment and/or prevention of epilepsy. One particular compound described therein is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine which is better know as lamotrigine.

It has now been surprisingly found that lamotrigine is particularly useful for treating and/or preventing migraine.

Accordingly, the present invention provides the use of lamotrigine and/or pharmaceutically acceptable salts thereof in the manufacture of a medicament in the treatment and/or prevention of migraine.

Lamotrigine and/or pharmaceutically acceptable salts thereof may be prepared according to the procedures described in EP-0 021 121.

The administration to a sufferer in need thereof may be by way of oral (including sub-lingual) or parenteral administration.

An amount effective to treat the disorders hereinbefore described depends on the usual factors such as the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 1 to 1000 mg, suitably 1 to 500 mg, for example an amount in the range of from 2 to 400 mg such as 2, 5, 10, 20, 30, 40, 50, 100, 200, 300 and 400 mg of the active compound. Unit doses will normally be administered once or more than once per day, for example 1, 2, 3, 4, 5 or 6 times a day, more usually 1 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 1 to 1000 mg, for example 1 to 500 mg, that is in the range of approximately 0.01 to 15 mg/kg/day, more usually 0.1 to 6 mg/kg/day, for example 1 to 6 mg/kg/day.

It is greatly preferred that lamotrigine is administered in the form of a unit-dose composition, such as a unit dose oral (including sub-lingual), rectal, topical or parenteral (especially intravenous) composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting

agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the compound and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prophylaxis of migraine which comprises lamotrigine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a further aspect the invention provides a method for the treatment and/or prophylaxis of migraine which comprises administrating an effective or prophylactic amount of lamotrigine to a sufferer in need thereof.

Such compositions may be prepared in the manner as hereinbefore described.

The following pharmacological data demonstrates the present invention.

Anti-Migraine Activity
Cortical Spreading Depression and Migraine

The above test as described by Wahl et al, 1987, Brain Research, **411**, 72-80 may be used to determine the anti-migraine activity of compounds such as lamotrigine or pharmaceutically acceptable salts thereof.

Animal Preparation

Experiments were performed in female or male cats (2.5-3.0 kg) which were fasted overnight with free access to water. Anaesthesia was induced with 4-5% halothane and maintained by intravenous administration of α-chloralose (90-110 mg/kg). Rectal temperature, and acid base status were maintained within the physiological range. The right femoral artery and veins were cannulated for measuring of blood pressure, arterial blood sampling and drug administration, respectively. Heart rate was also determined from the blood pressure signal and recorded. A left sided parietal bone craniotomy and durectomy was performed and the brain covered with a layer of prewarmed mineral oil at 37°C. Changes in vessel diameter were investigated with intravital videomicroscopy and recorded on video tape.

Induction of Cortical Spreading Depression

CSD was induced by administration of a small quantity (30 mg crystal) of KCl to a region of the suprasylvian gyrus distant from recording electrodes, vessels under observation and other blood vessels. As the brain is covered in a layer of warm mineral oil, the KCl dissolves slowly into the brain for the 6 min period of application. Following this time,

the remaining KCl was washed from the brain surface with a saline swab. Changes in extracellular potential and in artery and vein diameter were then recorded for a period of up to 120 min.

Drug Treatment

The compound lamotrigine (10 mg/kg, i.p.) or vehicle (labrasol i.p.) was administered 90 min before CSD induction.

KCl-induced reproducible CSD events in control animals (n=4) were monitored over the observation period. In contrast, in lamotrigine treated animals (n=2) only initial CSD events were detected in response to KCl application. The total median (min-max) number of CSD events in control and treated groups were 5.5 (4-9) and 2 (1-3), respectively.

Trigeminal nerve model in anaesthetised cats

In the model, adapted from that of Lambert G.A. et al (1984), J. Neurosurg. **61**, 307-315, cats were anaethetised with α-chloralose (90-110 mg/kg i.v.) and artificially respired with room air. Body temperature was maintained at 37-38°C. A femoral artery was cannulated for recording of blood pressure and heart rate. Arterial blood flow was recorded by a Doppler flow probe placed around the right common carotid artery. Bipolar stainless electrodes were stereotaxically placed into each trigeminal ganglion. Guanethidine (3 mg/kg i.v.) was then administered and 45 min allowed for stabilisation. Stimulation (2mA, 10 Hz for 2 min) of the trigeminal ganglion, ipsilateral to the carotid artery from which blood flow was measured, produced an increase in carotid blood flow and reduction in carotid vascular resistance. The ability of drugs, given intraduodenally to modulate this response was used to assess their effects on the trigemino-vascular system.

Intraduodenal administration of lamotrigine (10 mg/kg as 1% suspension in methylcellulose) produced a significant inhibition [34 ± 8.7% (n=3)] of TGN-induced reduction in carotid vascular resistance after 3 hours.

CLAIMS

1. Use of lamotrigine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment and/or prevention of migraine.

2. A method of treating or preventing migraine in humans which comprises administering to a patient in need thereof an effective amount of lamotrigine or a pharmaceutically acceptable salt thereof.

3. Use according to claim 1 or a method according to claim 2 wherein lamotrigine or a pharmaceutically acceptable salt thereof is administered in the form of a unit-dose composition.

4. A pharmaceutical composition for use in the treatment and/or prophylaxis of migraine which comprises lamotrigine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.